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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,717	11/22/2000	Aya Jakobovits	ABGX-001CON3	5842

7590

06/26/2002

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EXAMINER

MCKELVEY, TERRY ALAN

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 06/26/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/718,717

Applicant(s)

JAKOBOVITS ET AL.

Examiner

Terry Mckelvey

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 18 March 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 2-8 and 11-15 is/are pending in the application.
- 4a) Of the above claim(s) 8 and 13-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-7, 11, 12 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

*Handwritten signature and stamp:*  
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JAN 10 2003  
Part of Paper No. 9

**DETAILED ACTION**

***Election/Restriction***

Claims 8 and 13-15 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4 filed 6/28/01.

This application contains claims 8 and 13-15 drawn to an invention nonelected with traverse in Paper No. 4. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a mammalian cell having about 55 kb deletion, does not reasonably provide enablement for making a deletion in the entire range of 15 kb to 3000 kb. The specification does not enable any

Art Unit: 1636

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. This rejection is maintained for reasons of record set forth in Paper No. 6, mailed 9/7/01.

Applicants' arguments filed 3/7/02 have been fully considered but they are not deemed to be persuasive.

The claims are drawn to a method for obtaining a mammalian cell containing a genomic deletion of 15-3000 kb by homologous recombination with a construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of the region to be deleted and a mammalian cell prepared by such a method.

In order to practice the invention, one of skill must make a construct containing 5' and 3' regions of the wild-type gene and successfully introduce the construct into a mammalian cell and obtain by selection a homologous construct. In order to achieve this goal, one must also include the following intervening steps, that is a) identifying cells containing the deletion by selecting cells containing a selectable marker present in the construct, and b) recovering cells containing the deletion.

The state of the prior art was that a deletion up to 19.2 kb was made in ES cells at the *hprt* locus, occurring at the same frequency as smaller deletions (Zhang et al (AX), abstract). This reference also suggested that "If this observation can be generalized, a wide spectrum of genomic deletions can be made in

ES cells which may facilitate the analysis of gene function." (pages 2409-2410). Thus, from the data in the reference, that large deletions are detected as frequently as smaller deletions and that the result might be generalized, it suggests that larger deletions may be possible. However, a reference published a year and a half later, Ramirez-Solis et al (AP), teaches that "Small deletions (20 kb) have been generated in embryonic stem (ES) cells by conventional gene targeting, but the construction of larger deletions, inversions or duplications has not been possible." (page 720, paragraph 1). Thus, although Zhang et al suggest that a broad spectrum of deletions may be possible, Ramirez-Solis et al teach that a year and a half later, no larger deletions were made. Thus, these references show or suggest that smaller deletions, about 19 kb are possible, but larger deletions are unpredictable and the art fails to provide guidance or working examples of deletions greater than about 19 kb.

The guidance presented in the specification is limited to a construct comprising two regions of sequences which are homologous to the 5' and 3' flanking sequences of the region to be deleted in the wild-type locus, identifying cells containing the deletion by selecting cells containing a selectable marker present in the construct, and recovering the cells containing the deletion in order to obtain a mammalian cell containing a genomic deletion. The specification gives limited guidance to making a broad range of deletions, but this guidance is speculative (and

Art Unit: 1636

thus limited) because it is based upon a single working example of making a deletion in the claimed range, i.e. deletion of 55 kb of the mouse hprt gene in embryonic stem (ES) cells, although the art teaches the unpredictability of making large deletions.

The relative skill of those in the art is high.

The claims are broad in that a very wide range of deletions is being claimed: 50 kb to 3000 kb.

Therefore, in order to practice the full scope of the claimed invention, the skilled artisan would have to envision constructs to be used in the claimed homologous recombination method, test them in the claimed homologous recombination method, and if the method failed to isolate cells having deletions other than about 50-55 kb, envision modifications to the vectors or method, test the modifications, and repeat the unpredictable experimentation until cells containing deletions other than about 50-55 kb are isolated. Because of the state of the prior art, in which no larger than 20 kb deletions were made, the unpredictability in the art of generating large, 20 kb+ deletions, taught in the art even after the filing date of the instant application, the lack of guidance in either the art or the specification for making such large deletions (except for about a 50-55 kb deletion), and the lack of working examples (except for about a 50-55 kb deletion) in either the art or the specification (for deletions greater than 19.2 kb), it would require much unpredictable experimentation to practice the full

scope of the invention given the failure in the prior art. This experimentation would be undue.

*Response to Arguments*

The applicant argues that the specification provides ample guidance to practice the invention without undue experimentation. This argument is not persuasive for the following reasons. The cited art shows that use of conventional replacement gene targeting techniques to make deletions larger than about 19 kb was considered to be unpredictable in the art at the time of the invention. There is nothing in the specification which specifically teaches how to overcome the unpredictability so as to predictably create much larger deletions, up to about 3000 kb. All of the teachings in the specification appear to be directed to simply repeating the general teachings well known in the art concerning conventional replacement gene targeting to make genomic deletions, like that taught by the various references previously cited in the Office Action such as Zhang et al of record. The only difference is that the applicants claim larger deletions, including much larger deletions than previously achieved, or even demonstrated to be achievable, by the teachings of the specification. The only working example taught by the specification which is larger than that reported in the prior art was a deletion, 55 kb, that was not that much larger than previously achieved, as compared to the whole claimed range.

Art Unit: 1636

There simply are no direct teachings by the specification as to what specifically must be done to achieve the much larger deletions than the prior art and the working example in the application itself achieved.

The applicant argues that Ramirez-Solis did not state that it is not possible to generate larger deletions using the method described in the instant specification because Ramirez-Solis did not have access to the instant specification. This argument is not persuasive for the following reason. The negative teachings of Ramirez-Solis et al are directed to conventional gene targeting: "Small deletions (20 kb) have been generated in embryonic stem (ES) cells by conventional gene targeting, but the construction of larger deletions, inversions or duplications has not been possible." (page 720, paragraph 1). Conventional gene targeting is precisely what is being claimed in the instant claims: introducing a construct comprising two regions of sequences that are homologous to the 5' and 3' flanking regions of a wild type locus, identifying cells containing a deletion by selecting cells containing a selectable marker. The only difference is that the applicant limits the method to achieving deletions to include those much larger than obtained in the prior art, without teaching or claiming the actual modifications of the conventional techniques that would predictably achieve those claimed large deletions. Thus the negative teaching of Ramirez-Solis is very applicable because it shows the unpredictability of what the applicant simply claims (very large deletions using



Art Unit: 1636

conventional techniques) which the applicant asserts without any guidance in the specification which advances the art so as to teach one of skill in the art how to predictably achieve those large deletions. Thus, it did not matter that Ramirez-Solis did not have access to the instant specification, because the instant specification does not add any new teachings to the art that would enable Ramirez-Solis to predictably succeed in making the larger or much larger deletions as claimed.

The applicant argues that those skilled in the art could generate deletions in the 50 to 3000 kb size range, using the method as claimed, without undue experimentation, citing Kimber et al (1999). This argument is not persuasive for the following reason. Although Kimber et al use conventional replacement gene targeting techniques (as specifically stated in column 1 of page 2230 of the reference), which reads on the claimed invention because the applicant is broadly claiming a conventional replacement gene targeting technique with a size limitation beyond that shown in the prior art, Kimber et al definitely did not use the same specific method as the instant specification to achieve the larger deletion and thus this reference published after the priority date of the instant application is not evidence that the instant application is enabling for the claimed invention. Kimber et al teach: "Fifteen to twenty kilobases of flanking sequence at the distant ends of these BACs were cloned on either side of PGKneo and an HSV TK gene was placed on either side of the construct to allow for positive and negative

Art Unit: 1636

selection." (page 2230, column 1). It was this construct that was used to make a 150 kb deletion. Thus, this reference describes two critical differences from the teachings of the instant application: much larger regions of flanking sequences at both ends of the region to be deleted than is described in the instant application, and the specific use of two selectable markers that allow for both positive and negative selection, which was not specifically suggested in the instant application. Either, or both of these differences, which appear to be different from the conventional replacement gene targeting techniques, are what is responsible for overcoming the earlier failure in the art described by Ramirez-Solis, and which are not specifically taught by the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for reasons of record set forth in Paper No. 6, mailed 9/7/01 (and amended to remove references to claims no longer rejected as

necessitated by the applicant's amendment filed 3/7/02).  
Applicant did not specifically address the rejection of claims 11-12 and thus the rejection remains for reasons of record.

With regard to claim 11, the claim fails to recite positive process steps which clearly relate to the preamble, making the claims unclear because it is unclear whether the claimed method is what the preamble states or what the method steps actually result in.

#### ***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

Art Unit: 1636

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014.

NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

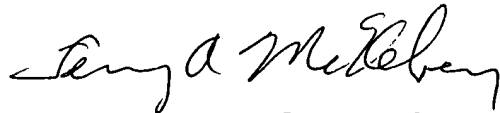
Any inquiry concerning missing attachments or other minor formalities of this communication should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 305-3291.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

Art Unit: 1636

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.  
Primary Examiner  
Art Unit 1636

June 25, 2002